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Japanese Published Unexamined (Kokai) Patent Application No. H2-53721, published February 22, 1990; Application No. S63-205380, filed August 18, 1988; Int. Cl.[5]: A61K 9/30; Inventor(s): Minoru Okada et al.; Assignee: SS Phermaceutical Corporation; Japanese Title: Hifuku Karyuu wo Fukumu Jouzai (Coating-applied Granule Containing Tablet)

Specification

1. Title of Invention

Coating-applied Granule Containing Tablet

2. Claim

(1) A coating-applied granule containing tablet obtained such that a coating-applied granule containing phermaceutical composition is compression-molded, characterized in that the coating-applied granules are further coated with a water-soluble or acid-soluble high molecular protecting film.

(2) A tablet, as disclosed in Claim 1, characterized in that the coating film of the coating-applied granules is made of one or two types from insoluble high molecules, enteric high molecules or various types of wax.

(3) A tablet, as disclosed in Claim 2, characterized in that an active phermaceutical is contained in the coating-applied granules.

(4) A tablet, as disclosed in any claim from Claim 1, Claim 2 and Claim 3, characterized in that the active phermaceutical is contained in the coating-applied granules and non-coating-applied granules.

3. Detailed Description of the Invention

[Field of Industrial Application]

This invention pertains to tablets molded by a compression means after coating-applied granules have been double-coated with water-soluble or acid-soluble high molecules. More specifically, this invention pertains to double-coated tablets wherein a breakage of the coating films of the coating-applied granules is prevented when coated granule containing phermaceutical compositions are compression-molded.

[Prior Art and the Problem of Prior Art to Be Addressed]

It is widely practiced that various functions such as a blocking or an anti-fusion of flavors and smells are added by applying enteric, acid-soluble or insoluble films on granules. These coating-applied granules are provided as they are or by being filled in hard or soft gelatin capsules. However, when the coating-applied granules are compression-molded into tablets, the functions of the films are often lost or change due to a breakage of the films by the compression force. Because of this, when tablet anti-fusible formulations are prepared, a coating is applied using insoluble high molecules in advance by predicting a breakage of the films due to a compression. By this means, granules wherein the diffusion is further controlled are formed. After this, tablets are obtained by applying a compression molding. However, the breakage of the films during the compression molding occurs by the film conditions and the properties of non-film sections. It is very difficult to predict the breakage. In many cases, the diffusion property of the obtained tablets differs from that predicted in advance.

[Measures to Solve the Problem]

In this situation, the inventors have eagerly studied on the breakage of the film when the coating-applied granules are compression-molded. As a result, the inventors have found that tablets obtained after a compression-molding has been applied to granules coated with water-soluble or acid-soluble high molecules can prevent the breakage of the film without loosing the property and the function of the coating-applied granules.

More specifically, the invention offers a coated granule containing tablet obtained such that a coated granule containing phermaceutical composition is compression-molded, characterized in that the coating-applied granules are further coated with a water-soluble or acid-soluble high molecular protecting film.

When the water-soluble or acid-soluble high molecules used for the invention are dosed into a living body, they function as a protection for the coating-applied granules so as to cope with the compression force during a compression process substantially without changing the function of the film of the coating-applied granules. For this reason, the protective film used for the invention is not limited to any types as long as they are the water-soluble or acid-soluble high molecules that function as described above. As for the water-soluble high molecules, the following types are used: hydroxy propyl methyl cellulose; hydroxy propyl cellulose; methyl cellulose; polyvinyl pyrrolidone; polyethylene glycol; gelatin. As for the acid-soluble high molecules, the following types can be given: an amino alkyl methacrylate copolymer E; polyvinyl acetal diethyl amino acetate. These high molecules can be used alone or by a combination of two or more types. If they can protect the coating-applied granules so as to cope with the compression force during the compression process substantially without

interrupting the function of the film of the coating-applied granules when they are dosed into a living body, they can be used as a mixture mixed with enteric and water-insoluble high molecules and various types of wax.

The amount of the water-soluble or acid-soluble high molecules used for the invention to be coated is not particularly limited to any amounts and determined according to the properties of the coating-applied granules and excipients that form the tablet. The amount is usually in the range of 5 to 50%.

When the tablet of the invention is produced, a coating of water-soluble or acid-soluble high molecules is applied to the granules by using a conventional method so as to produce double-coating applied granules. During the production, an applicable plasticizer, brightener and coloring agent can be added as needed. The double-coating applied granules are mixed with a widely known tablet forming composition that contains the following applicable agents as needed: an excipient; a binder; a disintegrator; a brightener; a coloring agent; a fragrance; a stabilizer.

In order to obtain an anti-diffusible or enteric film for the film of the coating-applied granules and a certain degree of the blood concentration immediately after the tablet has been dosed, an active phermaceutical can be mixed in the protective film or non-coating applied granular sections.

Furthermore, the tablet of the invention can be formed into the following types by using a conventional method: a core containing type; a multi-layer type; a film coating type; a sugar coating type.

[Effect and the Advantage]

The coated granule containing tablet of the invention as obtained above does not loose the function for the film of the coating-applied granules even when a compression molding is applied, due to an effect of a water-soluble or acid-soluble high molecular coating and demonstrates a certain effect.

[Embodiment]

The embodiments of the invention are described hereinbelow in detail.

Embodiment 1

Production of bare granules a:

By mixing sodium di-chlofenaku [Translator's note: the word is not located in any dictionaries] of 800 g and corn starch of 400 g and then by finely pulverizing the mixture, a micropowder is obtained. The micropowder is granulated by a rotating means while a liquid obtained by mixing hydroxy propyl cellulose of 25 g into ethyl alcohol of 475 g using white sugar of 600 g as a core, which is adjusted to a 28 to 35 mesh grain, is poured so as to produce spherical granules. The obtained spherical granules are dried at 55°C for 3 hours. The dried granules that fit into the passing range between 16 and 35 meshes are defined as bare granules a.

Embodiment 2

Production of coating-applied granules b:

Bare granules a of 800 g, which are produced as in Embodiment 1, are supplied into a fluid layer coater. A spray coating is applied applying a coating solution of 2746 g, which contains the following components at the following ratios by using a conventional method so as to produce coating-applied granules b:

Components	%
Methacrylate copolymer L	6.5
Talc	0.2
Ethyl alcohol	93.3
Total	100.0

The amount of granules coated is 23% in relation to amount of the bare granules.

Embodiment 3

Production of double-coating applied granules c:

Coating-applied granules b of 500 g, which is produced as in Embodiment 2, are supplied into the fluid layer coater. A spray coating is applied applying a coating solution of 1389 g, which contains the following components at the following ratios by using a conventional method so as to produce coating-applied granules c:

Components	%
Hydroxy propyl methyl cellulose	6.5
Macro Goal 6000	0.5
Talc	0.2
Ethyl alcohol	66.8
Purified water	27.0
Total	100.0

The amount of granules coated is 20% in relation to the amount of bare granules b.

Embodiment 4

Production of tablets of the invention:

A 10% (W/W) hydroxy propyl cellulose 50% ethyl alcohol solution of 125 g is added to a mixture powder of the following substances at the following weights: crystalline cellulose at 240 g; corn starch at 25 g; lactose at 172.5 g. This mixture is kneaded, and granules are produced by using a conventional method. After this, the following components at the following weights are evenly mixed: these granules at 203.6 g; double-coating applied granules c at 168.4 g, which are obtained as in Embodiment 3; calcium carboxy methyl cellulose at 20 g; magnesium stearate at 4 g; talc at 4 g. This mixture is then compression-molded so as to produce tablets of the invention at 400 mg per tablet, which has a 10 mm diameter.

Embodiment 5

Production of comparative tablets:

A 10% (W/W) hydroxy propyl cellulose 50% ethyl alcohol solution of 125 g is added to a mixture powder of the following substances at the following weights: crystalline cellulose at 240 g; corn starch at 25 g; lactose at 172.5 g. This mixture is kneaded, and granules are produced by using a conventional method. After this, the following components at the following weights are evenly mixed: these granules at 203.6 g; double-coating applied granules b at 140.3 g, which are obtained as in Embodiment 2; lactose at 28.1 g; calcium carboxy methyl cellulose at 20 g; magnesium stearate at 4 g; talc at 4 g. This mixture is then compression-molded so as to produce tablets of the invention at 400 mg per tablet, which has a 10 mm diameter.

Embodiment 6

The tablets of the invention obtained as in Embodiment 4, the comparative tablets obtained as in Embodiment 5 and coating-applied granules b are eluded so as to obtain eluates. Using a testing solution at 4.5 pH for 30 minutes from the beginning of the testing and a testing solution (a second solution; the 11th amendment of the Japanese Pharmacopoeia) at 6.6 pH after 30 minutes to 60 minutes, the eluates are measured at 100 r.p.m. by using a rotating puddle method (the 11th amendment of the Japanese Pharmacopoeia). The results are indicated in Table 1. No breakage is found in the film of the tablets of the invention unlike the comparative tablets. The same elution property as that of the comparative tablets is also demonstrated.

Table 1

Elapsing time (Minutes)	Elution rate (%)		
	Embodiment 4 (Invention)	Embodiment 5 (Comparative example)	Coating-applied granules b (Comparative example)
(Please refer to the original description)			

Embodiment 7

Production of bare granules d:

Using a solution obtained by dissolving the following substances at the following weights in ethyl alcohol of 475 g: theophylline at 800 g; corn starch at 375 g; white sugar at 600

g, which is granulated in 28 to 35 meshes; hydroxy propyl cellulose at 25 g, bare granules d are obtained using a method similarly to as in Embodiment 1.

Embodiment 8

Production of coating-applied granules e:

After bare granules d of 800 g, which are produced as in Embodiment 7, have been supplied into the fluid layer coater, a spray coating is applied using a coating solution of 1684 g, which contains the following components at the following ratios, based on a conventional method so as to produce coating-applied granules e:

Components	%
Ethyl cellulose	2.7
Polyvinyl pyrrolidone K30	0.9
Talc	0.2
Ethyl alcohol	66.8
Ethyl alcohol	96.2
Total	100.0

The amount of the granules coated is 8% in relation to the amount of the bare granules.

Embodiment 9

Production of double-coating applied granules f:

After coating-applied granules e of 600 g, which are produced as in Embodiment 8 have been supplied in the fluid layer coater, a spray coating is applied using a coating solution of 2000 g, which contains the following components at the following ratios, based on a conventional method so as to produce coating-applied granules f:

Components	%
Polyvinyl acetal diethyl amino acetate	6.0
Ethyl alcohol	47.0
Acetone	47.0
Total	100.0

The amount of these granules coated is 20% in relation to the amount of coating-applied granules e.

Embodiment 10

Production of tablets of the invention:

After the following substances at the following weights have been evenly mixed: double-coating applied granules f at 147.8 g; crystalline cellulose at 150 g; lactose at 46.2 g; magnesium stearate at 3 g; talc at 3 g, the mixture is compression-molded so as to produce tablets of the invention at 350 mg per tablet, which have a 9 mm diameter.

Embodiment 11

Production of comparative tablets:

After the following substances at the following weights have been evenly mixed: double-coating applied granules e at 123.2 g; crystalline cellulose at 150 g; lactose at 70.8 g; magnesium stearate at 3 g; talc at 3 g, the mixture is compression-molded so as to produce tablets at 350 mg per tablet, which have a 9 mm diameter.

Embodiment 12

The tablets of the invention obtained as in Embodiment 10, the comparative tablets obtained as in Embodiment 11 and coating-applied granules e are eluded so as to obtain eluates. Using a testing solution, the eluates are measured at 100 r.p.m. by using a rotating puddle method (the 11th amendment of the Japanese Pharmacopoeia). The results are indicated in Table 2. The tablets of the invention demonstrates an elution property similar to as that of the comparative granules, and the diffusion speed has not changed unlike that of the comparative tablets.

Table 2

Elapsing time (Hours)	Elution rate (%)		
	Embodiment 10 (Invention)	Embodiment 11 (Comparative example)	Coating-applied granules e (Comparative example)
(Please refer to the original description)			

Embodiment 13

Production of coating-applied granules g:

A solution obtained by dissolving hydroxy propyl cellulose of 40 g in ethyl alcohol of 760 g is added to a mixture powder of the following substances at the following weights: cephalexin at 1400 g; lactose at 160 g; purified white sugar at 200 g; crystalline cellulose at 200 g. This mixture is then kneaded. After the kneaded mixture has been granulated using a cylindrical granulator, spherical granules are produced using a marumerizer [Translator's note: the word is not located in any dictionaries] and then dried at 55°C for 2 hours. The dried granules that pass 16 meshes and that do not pass 35 meshes are defined as bare granules g.

Embodiment 14

Production of coating-applied granules h:

After supplying bare granules g of 800 g, which are produced as in Embodiment 13, in the fluid layer coater, a spray coating is applied using a coating solution of 3582 g, which contains the same components as those as in Embodiment 2, based on a conventional method so as to produce coating-applied granules h. The amount of the granules coated is 30% in relation to the amount of bare granules g.

Embodiment 15

Production of double-coating applied granules I:

After supplying coating-applied granules h of 400 g, which are produced as in Embodiment 14, in the fluid layer coater, a spray coating is applied using a coating solution of 1111 g, which contains the same components as those as in Embodiment 3, based on a conventional method so as to produce double-coating applied granules I. The amount of the granules coated is 20% in relation to the amount of coating-applied granules h.

Embodiment 16

Production of tablets of the invention:

A solution obtained by dissolving hydroxy propyl cellulose of 10 g in ethyl alcohol of 190 g is added to a mixture powder of the following substances at the following weights: cephalexin at 700 g; lactose at 90 g; purified white sugar at 200 g. After this mixture has been kneaded, it is dried at 55°C for 2 hours. The granules are produced by using the conventional

method. After the following components at the following weights have been evenly mixed: these granules at 53.6 g; double-coating applied granules I as in Embodiment 15 at 195 g; crystalline cellulose at 143.4 g; magnesium stearate at 4 g; talc at 4 g, the mixture is Embodime compression-molded so as to obtain tablets of the invention at 800 mg per tablet, which have a 13 mm diameter.

Embodiment 17

Production of comparative tablets:

A solution obtained by dissolving hydroxy propyl cellulose of 10 g in ethyl alcohol of 190 g is added to a mixture powder of the following substances at the following weights: cephalexin at 700 g; lactose at 90 g; purified white sugar at 200 g. After this mixture has been kneaded, it is dried at 55°C for 2 hours. The granules are produced by using the conventional method. After the following components at the following weights have been evenly mixed: these granules at 53.6 g; double-coating applied granules h as in Embodiment 14 at 162.5 g; crystalline cellulose at 143.4 g; lactose at 32.5 g; magnesium stearate at 4 g; talc at 4 g, the mixture is compression-molded so as to obtain tablets of the invention at 800 mg per tablet, which have a 13 mm diameter.

Embodiment 18

Production of comparative granules:

After bare granules g of 10.7 g and coating-applied granules h of 32.5 g have been mixed with each other, these mixture granules are separately packed at 432 mg each so as to

obtain a granular agent. nt 19

The tablets of the invention obtained as in Embodiment 16, the comparative tablets obtained as in Embodiment 17 and the comparative granular agent obtained as in Embodiment 18 are eluded so as to obtain eluates. Using a testing solution (a first solution; the 11th amendment of the Japanese Pharmacopoeia) at 1.2 pH for 30 minutes from the beginning of the testing and a testing solution (a second solution; the 11th amendment of the Japanese Pharmacopoeia) at 6.8 pH after 30 minutes to 60 minutes, the eluates are measured at 100 r.p.m. by using a rotating puddle method (the 11th amendment of the Japanese Pharmacopoeia). The results are indicated in Table 3. Whereas the tablets of the invention do not demonstrate any changes in the elution property in comparison with that of the comparative granular agent, the elution property of the comparative tablets significantly change.

Table 3

Elapsing time (Minutes)	Elution rate (%)		
	Embodiment 16 (Invention)	Embodiment 17 (Comparative example)	Embodiment 18 (Comparative example)
(Please refer to the original description)			

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